

## **REMARKS**

### **STATUS OF THE CLAIMS**

Claims 1-28 were pending in this application. Claims 1, 22, and 24-28 have been amended. Following entry of the amendments claims 1-28 will be pending and at issue.

### **SUPPORT FOR AMENDMENTS TO THE CLAIMS**

Claim 1 has been amended to clarify the term “direction.” Support for amendments to claim 1 are found throughout the specification as filed, e.g., paragraph [00119]. Claim 1 has further been amended to recite “recording a listing of the subset of genes identified.” Support for amendments to claim 1 are found throughout the specification as filed, including within the various tables of the specification that record a listings of identified subsets of genes within the concordance sets identified. Claim 22 has been amended to clarify the term “sign.” Support for amendments to claim 22 are found throughout the specification as filed, e.g., paragraph [00135]. In addition, certain typographical errors have been corrected in the claims. These changes are believed not to introduce new matter, and their entry is respectfully requested.

### **ELECTION/RESTRICTION REQUIREMENT**

Applicants note the Examiner’s indication that he is re-joining Groups I (claims 1-21) and II (claims 22-28). Thus, the Examiner indicated he will examine claims 1-28 and the elected species of Table 5.

### **IDS**

Applicant notes with appreciation the Examiner’s thorough consideration of the references cited in the IDS (Form 1449) submitted on December 9, 2003, December 22, 2003, April 15, 2005, and June 24, 2005. The Examiner indicated that he did not consider the PCT search report submitted with the IDS because it is not a published document.

Applicant respectfully submits that the PCT search report is a published document that is published on the WIPO website. Thus, Applicant respectfully requests that the Examiner consider this reference in his examination of the present application.

### **INTERVIEW SUMMARY**

Applicant's representative, Antonia Sequeira, attended a telephonic interview with the Examiner on September 6, 2006. The Examiner indicated that the Applicant could respond to the Examiner's arguments regarding 35 U.S.C. § 112, first and second paragraphs by submitting a sequence listing along with an statement to support the sequence listing attesting that the sequences included in the sequence listing are the sequences corresponding to the genes referred to in Table 5 (and other Tables), identified by the provided LocusLink identifiers and other descriptive data as of the earliest priority date of the present application. Thus, a sequence listing is submitted herewith, along with the Statement to Support Filing and Submission under 37 CFR 1.821-1.825 that includes as item #5 the attestation required by the Examiner that the "sequences in the attached Sequence Listing are those sequences that correspond to the sequences referenced in the specification of U.S. Utility application Serial Number 10/660,434 and that the provided sequences were available as of the September 10, 2002 priority date of that application." On December 7, 2006, Applicant's representative attended a telephonic interview with the Examiner to discuss the rejection under section 101. Applicant's representative suggested the language "recording a listing of the subset of genes identified" recited in amended claim 1 as possibly being sufficient to overcome the rejection. The Examiner agreed that this language might overcome the rejection and indicated he would consider this language.

## **SUBSTITUTE SPECIFICATION**

Since a number of amendments have been made to the specification herein, Applicant is submitting a substitute specification, including a copy showing markings indicating amendments made and a clean copy in accordance with 37 CFR § 1.125. Also, in accordance with 37 CFR § 1.125, Applicant states that the substitute specification includes no new matter.

The specification has been amended to delete the embedded hyperlinks as noted by the Examiner. Accordingly, Applicant respectfully requests that Examiner reconsider and withdraw the objection to the specification.

In addition, the specification has been amended to include sequence identifiers (SEQ ID NOS) in accordance with 37 CFR § 1.821 corresponding to sequences referenced in various Tables within the specification. For the few sequences referenced in the Tables that

are not included in the sequence listing, the corresponding information for these sequences has been deleted from the specification.

Applicant respectfully requests that the Examiner substitute this newly filed specification for the originally filed specification in this case, and make the amendments to the claims as shown in this response to the Office Action.

## **SEQUENCE LISTING**

Applicant includes herewith a Sequence Listing in computer readable form (1 disk labeled "CRF" and as a paper copy on CD-R, 2 copies (2 disks, labeled "Copy 1" and "Copy 2"). Applicant also submits herewith a Statement to Support Filing and Submission under 37 CFR § 1.821 – 1.825 that includes as item #5 the attestation required by the Examiner that the "sequences in the attached Sequence Listing are those sequences that correspond to the sequences referenced in the specification of U.S. Utility application Serial Number 10/660,434 and that the provided sequences were available as of the September 10, 2002 priority date of that application."

## **CLAIM OBJECTIONS**

Claims 24-28 were objected to as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants thank the Examiner for pointing this out and have corrected these typographical errors. Thus, Applicant requests withdrawal of this objection as drawn to the amended claims.

## **REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH**

Claim 1 was rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite because the Examiner stated that "it is unclear what the term 'direction' means in line 9." Office Action p. 4. Applicant has amended claim 1 to clarify this claim language. Specifically, claim 1 now recites "identifying a concordance set of expressed genes, said concordance set consisting of genes common to said first and second reference sets wherein the direction of said differential expression of *each of said common genes* is the same in said first and second reference sets" (emphasis added), thereby clarifying that the claim language refers to the first of the two interpretations suggested by the Examiner.

The Examiner further indicated that “there is insufficient antecedent basis for this limitation in the claim.” *Id.* The Applicant has corrected the antecedent basis issue and thanks the Examiner for pointing out this typographical error.

Claim 22 was rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite because the Examiner stated that “it is unclear what the term ‘the sign’ means.” Office Action p. 4. Applicant has amended claim 22 to clarify this claim language. Specifically, claim 22 now recites “correlating expression of said expressed genes with said phenotype by determining whether a sign of a second correlation coefficient is a negative or positive value...,” thereby clarifying that the claim language refers to the first of the two interpretations suggested by the Examiner.

The Examiner further indicated that “there is insufficient antecedent basis for this limitation in the claim.” *Id.* The Applicant has corrected the antecedent basis issue and thanks the Examiner for pointing out this typographical error.

Applicants have corrected these typographical errors and thus request withdrawal of this rejection as drawn to the amended claims.

Claims 22-28 were rejected under 35 U.S.C. § 112, second paragraph as unclear because “the recited tables include genes that are insufficiently described in the specification.” Office Action p. 4. The Examiner indicated that the “specification does not include any sequence listing that indicates what the gene is.” *Id.* Per the Examiner’s suggestion, Applicant is submitting with this Response a sequence listing along with an affidavit indicating that the sequences included in the sequence listing are in fact the sequences corresponding to the genes referred to in Table 5 (and other Tables) identified by the provided LocusLink identifiers and other descriptive data as of the earliest priority date of the present application. Accordingly, Applicants respectfully request withdrawal of this ground of rejection.

#### **REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH**

Claims 22-28 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner indicated that the “instant specification has no gene sequence” for the genes of Table 5. Office Action, p. 5. The Examiner indicated that the provided Affymetrix Probe Set IDs,

LocusLink Identifiers, and Descriptions of Table 5 are not sufficient, but instead Applicants “must provide a sequence listing of each gene in order for one of skill in the art to know that the inventor had possession of the claimed invention at the time the application was filed.” *Id.* at p. 6. In an interview with the Examiner on September 6, 2006, the Examiner indicated it would be sufficient for Applicant to now submit a sequence listing along with a statement attesting that the sequences included in the sequence listing are the sequences corresponding to the genes referred to in Table 5 (and other Tables) identified by the provided LocusLink identifiers and other descriptive data as of the earliest priority date of the present application. Thus, this sequence listing and the statement are included with this response. Accordingly, Applicants respectfully request withdrawal of this ground of rejection.

The Examiner further indicated that claims 24-28 were rejected under 35 U.S.C. § 112, first paragraph for failing to comply with the enablement requirement. For at least the reasons described above, claims 24-28 comply with the enablement requirement, and accordingly Applicants respectfully request withdrawal of this ground of rejection.

#### **REJECTIONS UNDER 35 U.S.C. § 101**

Claims 1-28 are rejected under 35 U.S.C. § 101 as allegedly directed to non-statutory subject matter. Applicant traverses this ground of rejection. The Examiner stated that the instant claims are “drawn to a mathematical algorithm of determining the correlation of gene expression data.” The Examiner concluded that the claims “do not include any tangible result” since they do not include “any step of conveying results to the real world.” The Applicant has amended claim 1 to include a step of “recording a listing of the subset of genes identified.” Thus, Applicant submits that claim 1 includes a tangible result, which is a step of conveying results to the real world (e.g., a listing of the subset of genes identified). Accordingly, the Applicant believes that the claims are directed to statutory subject matter and withdrawal of this ground of rejection is respectfully requested.

#### **REJECTIONS UNDER 35 U.S.C. § 103**

Claims 1-23 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Backert et al (Int. J. Cancer (1999) Volume 82, pages 868-874) in view of Bertucci et al.

(Human Molecular Genetics (2000) Volume 9, Number 20, pages 2981-2991). Applicant traverses this ground of rejection.

Three requirements must be met for a *prima facie* case of obviousness. First, the prior art references must teach all the limitations of the claims. Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention. Third, a reasonable expectation of success is required.

The cited prior art references do not teach all of the elements of the claims. Neither Backert nor Bertucci teach “identifying a first reference set of expressed genes” and “identifying a second reference set of expressed genes” of claim 1, where the first and second reference sets are derived independently from different samples. Backert described analysis of “expression of selected genes coding for proteins with defined cellular functions....in human cell lines derived from normal colonic mucosa, non-mucinous colonic mucosa, and mucinous colonic carcinomas,” and Backert observed “[a]ltered expression of 10 genes in colon carcinoma cells.” Backert, p. 868, Abstract. As noted by the Examiner, Backert further describes “[v]erification of the results obtained in the cell model system by Northern blots of RNAs obtained from human tissues” that yielded “only 2 correct positives out of 10 detected in the cell lines.” *Id.* at p. 871, right column, third full paragraph. Thus, Backert does not identify a first reference set of genes (differentially expressed between a first sample and a second sample), identify a second reference set of genes (differentially expressed between a third sample and a fourth sample) independent of the first reference set, and identify a concordance set of expressed genes with genes common to the first and second reference sets. Instead, Backert analyzes expression in cell lines and finds 10 genes with altered expression, and then verifies these results against samples taken from human tissues. Bertucci does not remedy this deficiency as Bertucci does not disclose identification of first and second reference sets as claimed.

Further, neither Backert nor Bertucci teach “identifying a subset of genes within said concordance set, wherein said subset is selected so that a first correlation coefficient, correlating for said genes within said subset a first expression differential between said first and second samples to a second expression differential between third and fourth samples, exceeds a predetermined value” of claim 1. While the Examiner indicated that Backert teaches identifying reference sets of genes and identifying a concordance set of genes, the

Examiner did not indicate where *identifying a subset of genes within said concordance set* is found in either Backert or Bertucci.

The Examiner further admitted that Backert does not teach “determining a correlation coefficient that exceeds a predetermined value,” but instead found that Bertucci teaches this part of the element, citing page 2987, right column, second full paragraph, of Bertucci in support. *See* Office Action, p. 9. However, this section of Bertucci only refers to a verification of the reproducibility of the array data before analysis of the results of the experiment. Bertucci described comparing duplicate spots on an array, comparing one hybridization with the same probe on two independent arrays, and compared two independent hybridizations with probes prepared from the same RNA. *See* Bertucci at page 2987, right column, second full paragraph. Bertucci indicated that the results showed “good reproducibility with respective correlation coefficients of 0.95, 0.98, and 0.98.” *Id.* Bertucci does not describe, for genes within an identified subset, the correlation coefficient correlating “a first expression differential between said first and second samples to a second expression differential between third and fourth samples.” Further, as stated above, neither Backert nor Bertucci even describe *identifying a subset of genes within said concordance set*, so they cannot describe identifying a subset of genes within a concordance set, *where that subset is selected so that a first correlation coefficient for that subset exceeds a predetermined value*.

Accordingly, the combination of Backert and Bertucci fails teach all of the elements of claim 1, and so cannot render independent claim 1 obvious, nor the claims that depend therefrom (claims 2-22). Therefore, withdrawal of this ground of rejection is respectfully requested.

The cited art further does not teach or provide a motivation to combine the teachings. The Examiner indicated that Backert recognized the need to determine the accuracy of gene expression experiments, and further indicated that Bertucci teaches determining the accuracy of gene expression using a correlation coefficient. Office Action p. 10. Thus, the Examiner concluded that since Backert recognizes the need for determining accuracy, and Bertucci provides for such a need, one of ordinary skill would be motivated to combine the methods to ensure accuracy of gene expression data. *See Id.* However, the method claimed in the present application is a method for identifying reference sets of expressed genes, identifying a concordance set consisting of genes common to the reference sets, and identifying a subset

of genes within the concordance set. This is not a method for verifying the reproducibility of gene expression experiments. Thus, one of skill in the art would not have thought to look to Bertucci's usage of a correlation coefficient for verification of experimental accuracy to be combined with the description in Backert to produce the claimed invention.

Accordingly, there is no motivation to combine the references as suggested by the Examiner, so withdrawal of this rejection is respectfully requested.

Claims 12 and 13 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Backert et al. in view of Bertucci et al. and further in view of Young et al. (US Publication No. 2005/0255588 A1). Claims 12 and 13 depend from claim 10, which depends from claim 9, which depends from claim 1. Thus, claims 12 and 13 incorporate all of the elements of claim 1. Therefore, claims 12 and 13 cannot be rendered obvious by the cited art for at least the reasons described above regarding claim 1. Accordingly, Applicant requests withdrawal of this rejection of claims 12 and 13.

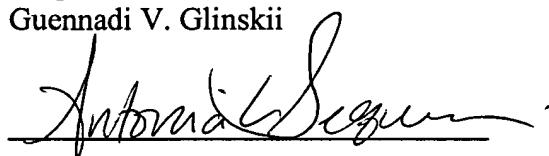
In conclusion, a *prima facie* case of obviousness has not been presented by the Office. Therefore, withdrawal of this ground of rejection of claims 1-22 is respectfully requested.

## CONCLUSION

Withdrawal of the pending rejections and reconsideration of the claims are respectfully requested, and a notice of allowance is earnestly solicited. If the Examiner has any questions concerning this Response, the Examiner is invited to telephone Applicant's representative at (650) 335-7185.

Respectfully Submitted,  
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